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Evaluation of risk factors that play roles in retinopathy of prematurity

Seda Gümüştekin[1], Şahin Takçı[2]
[1] Department of Pediatrics, Erciyes University, Kayseri
[2] Department of Pediatrics, Ondokuz Mayıs University, Samsun, Turkey

Abstract
Aim: Increasing survival rates of preterm babies have made it necessary to focus on complications of prematurity, such as retinopathy of prematurity (ROP). The present study aimed to investigate factors that may be involved in the development of ROP.
Material and Methods: Between February 2011 and March 2018, the medical records of babies born at 32 weeks of gestation or earlier and examined for ROP at Gaziosmanpaşa University, Neonatal Intensive Care Unit (NICU) were analyzed retrospectively. Risk factors that may be associated with the development of ROP in infants were determined.
Results: A total of 193 infants were included in the study. Mean gestational age at birth and birth weight were 30.1 ± 1.9 weeks and 1487 ± 395 grams, respectively. ROP was detected in 61 (34%) of the infants, and 11 (18.1%) of those required treatment. Comparison of the characteristics of infants with and without ROP showed that gestational age at birth, birth weight, need for positive pressure ventilation in the delivery room, need and number of blood transfusions, Patent Ductus Arteriosus (PDA), Intraventricular Hemorrhage (IVH), presence of Bronchopulmonary Dysplasia (BPD), hyperglycemia, hemoglobin and hematocrit levels at discharge, period of oxygen support, time to achieve full enteral nutrition, and length of hospital stay were significant factors related to the development of ROP. In multivariate logistic regression analyses, birth weight, gestational age at birth, and period of oxygen support were the only independent risk factors.
Discussion: It is extremely important to identify risk factors for ROP and to take timely preventive and therapeutic measures for better premature outcomes.

Keywords
Prematurity, Retinopathy of Prematurity, Risk Factors

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Corresponding Author: Seda Gümüştekin, Department of Pediatrics, Erciyes University, Kayseri, Turkey.
E-mail: seda_gumustekin89@hotmail.com P: +90 554 206 60 04
Corresponding Author ORCID ID: https://orcid.org/0000-0003-0738-4265

Introduction

Retinopathy of prematurity (ROP) is a disease of preterm infants characterized by abnormal proliferation of retinal vessels, the exact pathogenesis of which has not been fully elucidated [1]. Despite advances in neonatal care and management, ROP remains the leading cause of childhood vision impairment worldwide. Increasing survival rates of preterm infants due to developments in neonatal care have led to an increase in the rate of ROP, which can cause vision problems and blindness. Although the pathogenesis of ROP has not been fully elucidated, it is thought to develop in a two-stage process. Retinal vascularization, which begins in the intrauterine environment delays after premature birth (Phase 1), whereas the retina continues to develop. The oxygen demand of the retina in which vascularization has delayed is not met and it becomes hypoxic. This hypoxia in the retina initiates the second phase [1–3].

Studies on the etiology of ROP have reported various risk factors covering the perinatal period to date [1–5]. It is extremely important to establish the frequency and risk factors for each NICU to develop appropriate preventive strategies and to have better premature outcome. The present study investigated the frequency and risk factors of ROP in premature infants followed up in our NICU.

Material and Methods

Between February 2011 and March 2018, the medical records of babies born at 32 weeks of gestation or earlier were examined for ROP in the NICU of Gaziosman Paşa University University were retrospectively reviewed. The first examinations were performed in the NICU at 4–6 weeks after birth or 31–33 weeks postconception. Ophthalmological follow-up was performed in the ophthalmology department. The most advanced ROP stage was taken into account for this study. The study was approved by the Institutional Ethics Committee (approval number: 2018/03: 83116987-161).

Delivery type, birth percentile, period of oxygen support, development of proven sepsis, maternal risk factors, Apgar scores at 1 and 5 min, number of transfusions, development of intraventricular hemorrhage (IVH), presence of Patent Ductus Arteriosus (PDA), presence of bronchopulmonary dysplasia (BPD), multiple pregnancy, and length of hospital stay were recorded. Daily blood glucose levels in the first 24 hours and hematologic parameters at discharge were noted. Maternal demographic data and risk factors were also recorded. The babies were divided into premature infants with and without ROP, and risk factors were compared between the two groups.

Data for continuous variables are shown as the mean ± standard deviation (SD) or median (interquartile range). Data for categorical variables are shown as numbers (%). Differences in continuous variables between groups were analyzed using the independent samples t test, Mann–Whitney U test, or one-way analysis of variance (ANOVA), and categorical variables were compared using Kruskal–Wallis variance analyses or the x2 test. The relations between numerical values were evaluated via Pearson's correlation analyses. Logistic regression analyses were used to examine causal relationships between dependent variables and independent variables when the outcome (dependent) variable was binary (binary/dichotomous). Statistical analyses were performed using IBM SPSS Statistics 19 (SPSS Inc., Somers, NY). In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

A total of 402 infants were examined for ROP during the study period, and 193 of those whose medical records were completely accessible were included in the study. Overall, 96 (49.7%) were female. The mean gestational age at birth and birth weight were 30.1 ± 1.9 weeks and 1487 ± 395 g, respectively. ROP was detected in 61 (34.6%) of the infants. Figure 1 shows the percentages of ROP development zones and stages. Four of the patients with ROP had plus disease. Eleven (18.1%) of the infants received treatment. Comparison of characteristics of the infants with and without ROP indicated that gestational age at birth, birth weight, application of positive pressure ventilation at birth, need and number of blood transfusions, PDA, IVH, presence of BPD, presence of hyperglycemia, hemoglobin

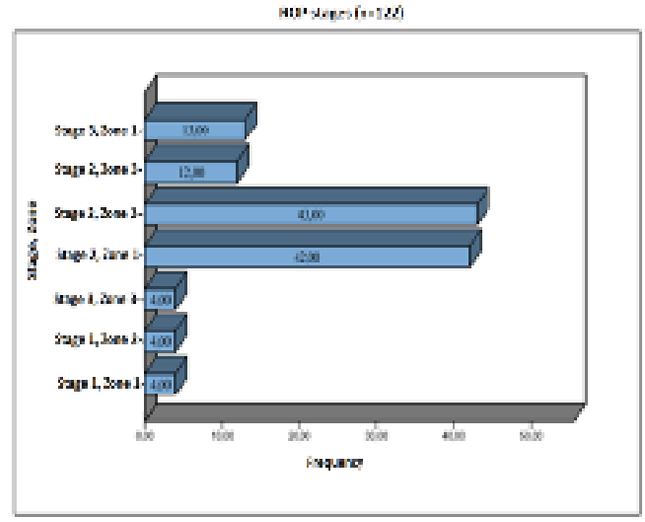

Figure 1. Frequency of ROP zones and stages

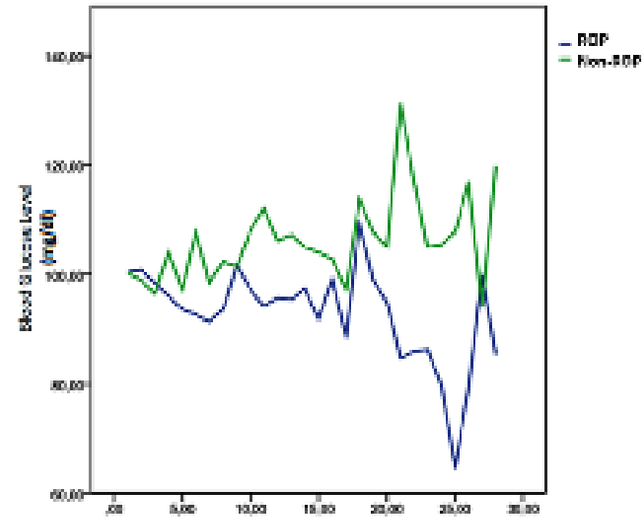

Figure 2. Average daily blood glucose monitoring in the first 28 days in infants with and without ROP

and hematocrit levels at discharge, period of oxygen support, transition to enteral nutrition, and length of hospital stay were significant factors for the development of ROP (Table 1). The mean glucose level in the first 28 days was 106 ± 7.9 mg/dL in infants with ROP, and 92.1 ± 10.5 mg/dL in those without ROP (p < 0.001) (Figure 2).

Maternal demographic data and risk factors were compared between the two groups, and no significant effects of multiple pregnancy, use of assisted reproductive techniques, smoking during pregnancy, prepregnancy body mass index (BMI), parity, gestational age, premature rupture of membranes, chorioamnionitis, gestational hypertension, or preeclampsia on the development of ROP were found (Table 2).

The risk factors affecting the development of ROP were evaluated via multivariate logistic regression analyses, and birth weight (odds ratio [OR]: 0.997; 95% confidence interval [CI]: 0.996–999), gestational age at birth (OR: 0.691; 95% CI: 0.530–0.880), and period of oxygen support (OR: 0.703; 95% CI: 0.522–0.881) were identified as independent risk factors (Table 3).

Table 1. Comparison of risk factors and characteristics of the infants with and without ROP

Infant Characteristics and Risk Factors		ROP	Without ROP	P
GA	<29 Weeks	5(%50)	5(%50)	<0,001
	≥29 Weeks	177(%96,7)	6(%3,3)	
BW	<1000	3(%17,6)	14(%82,4)	<0,001
	1000 – 1499	50(%56,8)	38(%43,2)	
	≥1500	80(%90,9)	8(%9,1)	
Apgar scores at 1min	0-6	55(%64,7)	30(%35,3)	0,259
	7 and over	59(%72,8)	22(%27,2)	
Apgar Scores at 5 min	0-6	20(%55,6)	16(%44,4)	0,086
	7 and over	94(%72,3)	36(%27,7)	
Positive Pressure Ventilation at Birth	Yes	59(%85,5)	10(%14,5)	<0,001
	No	69(%58)	50(%42)	
Gram Positive or Negative Positive Blood Cultures	No Reproduction	129(%73,2)	47(%26,7)	0,262
	Gram (-)	3(%50)	3(%50)	
	Gram (+)	15(%57,69)	11(%42,31)	
Blood Transfusions	Yes	90(%79,6)	23(%20,4)	<0,001
	No	39(%50,6)	38(%49,4)	
Number of Blood Transfusions	1	19(%52)	16(%48)	<0,001
	2 and over	12(%26,9)	30(%73,1)	
PDA	Negative	111(%74,5)	38(%25,5)	0,002
	Positive	17(%54,84)	14(%45,16)	
IVH	Negative	114(%74,03)	40(%25,97)	<0,001
	Positive	13(%39,39)	20(%60,61)	
BPD	Negative	115(%76,16)	36(%23,84)	<0,001
	Positive	10(%30,3)	23(%69,7)	
Hyperglycemia: Serum glucose ≥125 (mg/dL)	No	89(%80,9)	21(%19,1)	<0,001
	Yes	43(%51,8)	40(%48,2)	
Hemoglobin levels at discharge (g/dL)	-	11,9 [9,4-13,7]	9,8 [8,5-11]	<0,001
Hematocrit levels at discharge (%)	-	34 [26,9-39]	27,2 [24,8-33]	<0,001
Platelet levels at discharge (mm3)	-	306 [248-429]	350 [271-479]	0,124
Period of Oxygen Support (day)	-	8 [4-16]	9 [5-19]	<0,001
Weight Gain on Day 28	-	300,7±180,9	321,1±185,5	0,525
Transition to Enteral Nutrition (day)	-	17,8±8,4	10,7±6,4	<0,001
Length of Hospital Stay (day)	-	48,4±20,3	28±15,2	<0,001

BW: birth weight (grams); GA: gestational age (weeks); PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; [1]Chi-square test, P < 0.01.

Discussion

In recent years, the number of preterm births has gradually increased due to the development of assisted reproductive techniques, and survival rates of low-birth-weight infants have increased with advances in neonatology. As a result, the incidence of ROP is gradually increasing [2]. The most important risk factor for ROP is immaturity as determined by low gestational age and birth weight. Other risk factors include oxygen toxicity, acidosis, IVH, PDA, sepsis, hyperbilirubinemia, low Apgar scores, mechanical ventilation, and the requirement for blood transfusion [2–7].

Many studies have shown that the frequency of ROP increases with the degree of prematurity. In a study population of 6998 babies conducted by the ET-ROP study group, the incidence

Table 2. Comparison of maternal risk factors according to ROP

Maternal Risk Factors		ROP	Without ROP	P
Use of Assisted Reproductive Techniques	No	126(%71,6)	50(%28,4)	0,208
	Yes	9(%52,9)	8(%47,1)	
Multiple Pregnancy	No	110(%71,9)	43(%28,1)	0,376
	Yes	25(%62,5)	15(%37,5)	
Smoking During Pregnancy	No	119(%67,6)	57(%32,4)	0,68
	Yes	4(%57,1)	3(%42,9)	
Prepregnancy Body Mass Index BMI	Normal	6(%54,5)	5(%45,5)	0,343
	Over-weight	2(%25)	6(%75)	
	Obese	3(%60)	2(%40)	
Parity	1	39(%70,9)	16(%29,1)	0,762
	>1	93(%67,4)	45(%32,6)	
Gestational Age	Young Mother Age	1(%50)	1(%50)	0,824
	Normal Maternal Age	103(%69,1)	46(%30,9)	
	Advanced Mother Age	28(%66,7)	14(%33,3)	
Premature Membrane Rupture	Negative	101(%66,5)	51(%33,5)	0,66
	Positive	19(%73,1)	7(%26,9)	
Chorioamnionitis	Negative	113(%66,9)	56(%33,1)	0,179
	Positive	6(%100)	-	
Gestational Hypertension	Negative	107(%66,9)	53(%33,1)	0,999
	Positive	14(%66,7)	7(%33,3)	
Preeclampsia	Negative	107(%68,6)	49(%31,4)	0,728
	Positive	21(%63,6)	12(%36,4)	
Eclampsia	Negative	126(%68,8)	57(%31,2)	0,032
	Positive	-	3(%100)	

Table 3. Analysis of independent risk factors associated with ROP

	OR	P	%95 Confidence interval
BW	0,997	<0,001	0,996-0,999
GA	0,691	0,004	0, 53 -0,88
Period of Oxygen Support (day)	0,703	0,045	0,522-0,881

BW: birth weight (grams); GA: gestational age (weeks)

of ROP was reported to be 89% in babies born at ≤27 weeks, 52.7% in babies born at 28–31 weeks, and 14.2% in babies born at ≥32 weeks [8]. The multicenter TR-ROP study conducted in Turkey in a population of 6115 babies indicated that the rate of severe ROP in babies born before gestational week 28 was 21.6%, and 2.2% in those born between 29 and 32 weeks [9]. In the same study, it was reported that ROP developed in 67 babies at 33 weeks or later. In the present study, the ROP rate in babies born before 32 weeks was 34.6%. Therefore, broad range of ROP screening criteria could be considered in Turkey.

In the CRYO-ROP study, the incidence of ROP was 65.8% in babies weighing less than 1251 g and 81.6% in those weighing less than 1000 g [10]. A multicenter study conducted in Turkey showed an incidence of ROP of 42% in infants with a birth weight of 1500 g or less compared to 14.5% in those with birth weight of 1501–2000 g. In addition, 8.2% of babies with a birth weight of 1000 g or less and 0.6% of babies with a birth weight above 1500 g were diagnosed with severe ROP [11]. In the present study, the incidence and severity of ROP increased with decreasing birth weight and gestational age.

With regard to the relationship between ROP and period of oxygen support, Huang et al. examined 108 premature babies with birth weight below 2000 g and found that the ROP group had a longer period of oxygen support and required a longer period of mechanical ventilation than the non-ROP group [12]. In the SUPPORT study, when high (91–95%) and low (85–89%) oxygen saturations were compared in babies born between 24 and 28 weeks, the mortality rate was found to increase in the low oxygen saturation group, while the rate of severe ROP in survivors was decreased [13]. Many later studies have been conducted to determine the effects of oxygen support on ROP, and most have found that high-level oxygen support is associated with increases in the incidence and severity of ROP. Although oxygen support is among the definite risk factors of ROP, no definitive data are available on how the concentration and period of oxygen support affect ROP. In the present study, the incidence and severity of ROP increased with increasing period of oxygen support.

Poor weight gain after birth is an indicator of poor health status in newborn infants. Aydemir et al. reported that babies with severe ROP gained 6.7 ± 4 g/day in the first 4 weeks of their lives, while those of normal weight and without ROP gained 9.3 ± 4.5 g/day, and they concluded that poor weight gain at 4 weeks was the result of various comorbidities rather than being an independent risk factor [14]. In addition, insufficient nutrition from energy and protein may cause a decrease in the plasma level of IGF-I [15]. The provision of sufficient energy from parenteral and enteral sources in the first 4 weeks of life is effective for reducing the risk for severe ROP in extremely premature infants [15]. In the present study, the mean weight gain on day 28 in patients without ROP was 321.1 g, while it was only 300.7 g in patients with PR, but the difference was not statistically significant.

The rate of transition of patients to full enteral nutrition is an important parameter affecting an infant's growth and development. Proper parenteral and enteral nutrition is essential for good developmental progress. Early transition to full enteral feeding can also be effective for reducing various risk factors that may affect the development of ROP. In a study conducted in North America, the long-term use of total parenteral nutrition was shown to increase the risk of developing ROP regardless of weight gain [16]. In a cohort study conducted in Egypt, long-term parenteral nutrition was identified as a risk factor for the development of ROP [17]. In the present study, the transition time to full enteral nutrition was 17.8 ± 8.4 days in infants with ROP and 10.7 ± 6.4 days in those without ROP. The development and severity of ROP increased with increasing time to transition to full enteral nutrition ($p < 0.05$).

Hyperglycemia seen in very-low-birth-weight infants is an important risk factor in mortality and morbidity of premature babies, particularly in the first week of life [18]. Premature babies are born with a lower IGF-I level than term babies [19]. IGF-I has an anti-insulin resistance effect, and therefore hyperglycemia in premature infants may be a clinical presentation of low IGF-I [19]. A meta-analysis conducted showed that hyperglycemia was significantly associated with ROP. However, in further analyses, this relationship disappeared after correcting for other factors [20]. In Garg et al., the mean glucose level in the first 3 days of life in infants with ROP was 103 ± 4 mg/dL, while it was 89 ± 36 mg/dL in those that did not develop ROP, and the relationship between hyperglycemia and ROP was significant [21]. In the present study, the mean glucose level at 28 days was 106 ± 7.9 mg/dL in the ROP group, while it was 92.1 ± 10.5 mg/dL in the non-PR group ($p < 0.001$). Thus, the frequency of ROP was higher in babies with hyperglycemia.

Conclusion

Although many risk factors for the development of ROP were identified in the present study, only low gestational age, low birth weight, and longer period of oxygen support were determined to be independent risk factors. It is extremely important to identify the risk factors for ROP and to take timely preventive and therapeutic measures for better premature outcomes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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